are euthanized, and the ascitic cells removed through the abdominal wall with a 20 g needle. The cells used for experiment are used within passage 3-20. After 20 passages in the mice, new cells are brought up from the frozen stock in liquid nitrogen, and mice are inoculated. For experiments, cells are rinsed with Hanks Balanced Salt Solution, counted on a haemocytometer and diluted with HBSS to a concentration of 2 x 10^6 cells/mL.

[0269] Study groupings are performed randomly after all mice have been administered tumor cells. The required groupings are similar to what is performed for solid tumor studies (see Example 26).

[0270] Mice are injected intravenously or intraperitonealy with the required volume of sample to administer the prescribed dose (10 μL/g as indicated) to the animals based on individual mouse weights. With intraperitoneal tumors, administrations generally begin 1-day post tumor cell inoculation.

[0271] Animal well-being is closely monitored daily. Signs of ill health and progression of morbidity are closely monitored as described in Example 26. Animals are weighed at the time of examination.

[0272] Upon termination of any mice, gross necropsies are performed to evaluate the extent of tumor burden and/or physiologically observable changes in organ appearances. Findings are recorded.

[0273] Group body weights are recorded Monday through Friday during the efficacy study for a period of 14 days after the last dosing.

[0274] All animals are observed at least once a day, more if deemed necessary, during the pre-treatment and treatment periods for mortality and morbidity. In particular, signs of ill health are based on body weight loss, change in appetite, behavioral changes such as altered gait, lethargy and gross manifestations of stress. Should signs of severe toxicity or tumor-related illness be seen, the animals are terminated (CO_2 asphyxiation) and a necropsy is performed to assess other signs of toxicity. Moribund animals must be terminated for humane reasons and the decision to terminate will be at the discretion of the animal care technician and the study manager. These findings are recorded as raw data and the time of death is logged on the following day.

[0275] Data is presented in tables or figures and includes mean body weights for each group as a function of time and increase in life-span.

Claims

1. A pharmaceutical composition for parenteral administration, comprising particulate delivery vehicles having associated therewith at least a first antineoplastic agent and a second antineoplastic agent, wherein said first and second agents are in a mole ratio which exhibits a non-antagonistic cytotoxic or cytostatic effect and wherein said first and second agents are associated with the delivery vehicles to maintain a non-antagonistic ratio in the blood on administration.

2. The composition of claim 1 wherein said delivery vehicles are 4 to 6,000 nm in diameter.

3. The composition of claim 1 or 2 wherein said delivery vehicles have a mean diameter of between 4.5 and 500 nm.

4. The composition of claim 3 wherein said vehicles have a mean diameter of less than 250 nm.

5. The composition of claim 1 wherein said delivery vehicles are from 4μm to 50μm in diameter.

6. The composition of any of claims 1 to 5 wherein said delivery vehicles comprise
   lipid carriers, and/or
   liposomes, and/or
   lipid micelles, and/or
   lipoprotein micelles, and/or
   lipid-stabilized emulsions, and/or
   cyclodextrins, and/or
   block copolymer micelles, and/or
   polymer microparticles, and/or
   polymer nanoparticles, and/or
   polymer lipid hybrid systems, and/or
   derivatized single chain polymers.

7. The composition of any one of claims 1 to 6 wherein said first and second agents are co-encapsulated.

8. The composition of any one of claims 1 to 7 wherein said mole ratio of the first agent to the second agent exhibits

a non-antagonistic cytotoxic or cytostatic effect to relevant cells in culture over at least 5% of the concentration range where >1% of the cells are affected in an *in vitro* assay for said cytotoxic or cytostatic effect.

9. The composition of claims 8 wherein said non-antagonistic effect is exhibited over at least 5% of the concentration range such that 10-90% of the cells are affected in said *in vitro* assay.

10. The composition of claim 9 wherein said non-antagonistic effect is exhibited over at least 5% of the concentration range such that 20-80% of the cells are affected in said *in vitro* assay.

11. The composition of claim 10 wherein said non-antagonistic effect is exhibited over at least 20% of the concentration range such that 20-80% of the cells are affected in said *in vitro* assay.

12. The composition of any of claims 1 to 11 which, when administered to a subject, provides a therapeutic activity greater than that which is obtained when said agents are administered in the same ratio but not associated with delivery vehicles.

13. The composition of any one of claims 1 to 12 wherein at least one of the agents is selected from the group consisting of a DNA damaging agent, a DNA repair inhibitor, a topoisomerase I inhibitor, a topoisomerase II inhibitor, a cell checkpoint inhibitor, a CDK inhibitor, a receptor tyrosine kinase inhibitor, a cytotoxic agent, an apoptosis inducing agent, an antimetabolite, a cell cycle control inhibitor, a therapeutic lipid, a telomerase inhibitor, an anti-angiogenic agent, a mitochondrial poison, a signal transduction inhibitor and an immunoagent.

14. The composition of claim 13 wherein the first agent is a cytotoxic agent and the second agent is a cell-cycle inhibitor, or
wherein the first agent is a DNA damaging agent and the second agent is a DNA repair inhibitor, or
wherein the first agent is a topoisomerase I inhibitor and the second agent is a S/G_2- or a G_2/M- checkpoint inhibitor, or
wherein the first agent is a G_1/S checkpoint inhibitor or a cyclin-dependent. kinase inhibitor and the second agent is a G_2/M checkpoint inhibitor, or
wherein the first agent is a receptor kinase inhibitor and the second agent is a cytotoxic agent, or
wherein the first agent is an apoptosis-inducing agent and the second agent is a cytotoxic agent, or
wherein the first agent is an apoptosis-inducing agent and the second agent is a cell-cycle control agent, or
wherein the first agent is a telomerase inhibitor and the second agent is a cell-cycle control inhibitor, or
wherein the first and second agents are antimetabolites, or
wherein the first and second agents are cytotoxic agents, or
wherein the first agent is a therapeutic lipid and the second agent is a cytotoxic agent, or
wherein the first agent is a topoisomerase I inhibitor and the second agent is a DNA repair inhibitor, or
wherein the apoptosis-inducing agent is a serine-containing lipid.

15. The composition of claim 14
wherein the first agent is irinotecan and the second agent is 5-FU or FUDR, or
wherein the first agent is cisplatin (or carboplatin) and the second agent is 5-FU or FUDR, or
wherein the first agent is idarubicin and the second agent is AraC or FUDR, or
wherein the first agent is oxaliplatin and the second agent is 5-FU or FUDR, or
wherein the first agent is irinotecan and the second agent is cisplatin (or carboplatin), or
wherein the first agent is gemcitabine and the second agent is cisplatin (or carboplatin), or
wherein the first agent is methotrexate and the second agent is 5-FU or FUDR, or
wherein the first agent is paclitaxel and the second agent is cisplatin (or carboplatin), or
wherein the first agent is etoposide and the second agent is cisplatin (or carboplatin), or
wherein the first agent is docetaxel or paclitaxel and the second agent is doxorubicin, or
wherein the first agent is doxorubicin and the second agent is vinorelbine, or
wherein the first agent is carboplatin and the second agent is vinorelbine, or
wherein the first agent is 5-FU or FUDR and the second agent is gemcitabine.

16. The composition of claim 15 wherein the first agent is irinotecan and the second agent is 5-FU or FUDR or wherein the first agent is cisplatin (or carboplatin) and the second agent is 5-FU or FUDR.

17. A method to prepare a composition of claim 1, which method comprises

a) determining in a relevant cell culture assay for cytotoxic or cytostatic activity a mole ratio of said first and

second agent which is non-antagonistic over at least 5% of the concentration range over which greater than 1% of cells are affected by said ratio of agents, and
b) encapsulating with said delivery vehicles a mole ratio of agents determined to be non-antagonistic in step a).

18. The method of claim 17 wherein said non-antagonistic effect is exhibited over at least 5% of the concentration range such that 10 - 90% of the cells are affected in said *in vitro* assay.

19. The method of claim 18 wherein said non-antagonistic effect is exhibited over at least 5% of the concentration range such that 20 - 80% of the cells are affected in said *in vitro* assay.

20. The method of claim 19 wherein said synergistic effect is exhibited over at least 20% of the concentration range such that 20 - 80% of the cells are affected in said *in vitro* assay.

21. The method of any of claims 17 to 20, wherein said determining employs testing at least one ratio of said agents at a multiplicity of concentrations and applying an algorithm to calculate a synergistic, additive, or antagonistic effect for said ratio over a range of concentrations.

22. The method of claim 21 which employs testing a multiplicity of ratios, and wherein said algorithm is the Chou-Talalay median effect method.

23. The method of any of claims 17 to 22 wherein at least one of the agents is selected from the group consisting of a DNA damaging agent, a DNA repair inhibitor, a topoisomerase I inhibitor, a topoisomerase II inhibitor, a checkpoint inhibitor, a CDK inhibitor, a receptor tyrosine kinase inhibitor, a cytotoxic agent, an apoptosis inducing agent, an antimetabolite, a cell cycle control inhibitor, a therapeutic lipid, a telomerase inhibitor, an anti-angiogenic agent, a mitochondrial poison, a signal transduction inhibitor and an immunoagent.

24. The method of claim 23 wherein the first agent is a cytotoxic agent and the second agent is a cell-cycle inhibitor, or
wherein the first agent is a DNA damaging agent and the second agent is a DNA repair inhibitor, or
wherein the first agent is a topoisomerase I inhibitor and the second agent is a S/G_2 - or a G_2/M- checkpoint inhibitor, or
wherein the first agent is a G_1/S checkpoint inhibitor or a cyclin-dependent kinase inhibitor and the second agent is a G_2 /M checkpoint inhibitor, or
wherein the first agent is a receptor kinase inhibitor and the second agent is a cytotoxic agent, or
wherein the first agent is an apoptosis-inducing agent and the second agent is a cytotoxic agent, or
wherein the first agent is an apoptosis-inducing agent and the second agent is a cell-cycle control agent, or
wherein the first agent is a telomerase inhibitor and the second agent is a cell-cycle control inhibitor, or
wherein the first and second agents are antimetabolites, or
wherein the first and second agents are cytotoxic agents, or
wherein the first agent is a therapeutic lipid and the second agent is a cytotoxic agent, or
wherein the first agent is a topoisomerase I inhibitor and the second agent is a DNA repair inhibitor, or
wherein the apoptosis-inducing agent is a serine-containing lipid.

25. The method of claim 24
wherein the first agent is irinotecan and the second agent is 5-FU or FUDR, or
wherein the first agent is cisplatin and the second agent is 5-FU or FUDR, or
wherein the first agent is idarubicin and the second agent is AraC or
wherein the first agent is oxaliplatin and the second agent is 5-FU or FUDR, or
wherein the first agent is irinotecan and the second agent is cisplatin (or carboplatin), or
wherein the first agent is gemcitabine and the second agent is cisplatin (or carboplatin), or
wherein the first agent is methotrexate and the second agent is 5-FU or FUDR, or
wherein the first agent is paclitaxel and the second agent is cisplatin (or carboplatin), or
wherein the first agent is etoposide and the second agent is cisplatin (or carboplatin), or
wherein the first agent is docetaxel or paclitaxel and the second agent is doxorubicin, or
wherein the first agent is adriamycin and the second agent is vinorelbine, or
wherein the first agent is carboplatin and the second agent is vinorelbine, or
wherein the first agent is 5-FU or FUDR and the second agent is gemcitabine.

26. The method of claim 25 wherein the first agent is irinotecan and the second agent is 5-FU or FUDR, or
wherein the first agent is cisplatin and the second agent is 5-FU or FUDR.

27. A composition according to any one of claims 1 to 16, for use in the treatment of a disease condition in a subject.

28. The composition of claim 27 wherein the subject is a human.

29. The composition of claim 27 wherein the subject is a non-human mammal or avian.

Patentansprüche

1. Pharmazeutische Zusammensetzung zur parenteralen Verabreichung, die partikulierte Abgabevehikel umfasst, die damit assoziiert wenigstens ein erstes antineoplastisches Mittel und ein zweites antineoplastisches Mittel haben, wobei das erste und das zweite Mittel in einem Molverhältnis sind, das eine nicht-antagonistische, cytotoxische oder cytostatische Wirkung aufweist, und wobei das erste und zweite Mittel mit den Abgabevehikeln assoziiert sind, um bei Verabreichung ein nicht-antagonistisches Verhältnis im Blut aufrecht zu erhalten.

2. Zusammensetzung nach Anspruch 1, wobei die Abgabevehikel einen Durchmesser von 4 bis 6.000 nm haben.

3. Zusammensetzung nach Anspruch 1 oder 2, wobei die Abgabevehikel einen mittleren Durchmesser zwischen 4,5 und 500 nm haben.

4. Zusammensetzung nach Anspruch 3, wobei die Vehikel einen mittleren Durchmesser von weniger als 250 nm haben.

5. Zusammensetzung nach Anspruch 1, wobei die Abgabevehikel einen Durchmesser von 4 μm bis 50 μm haben.

6. Zusammensetzung nach einem der Ansprüche 1 bis 5, wobei die Abgabevehikel umfassen:

   Lipidträger und/oder
   Liposome und/oder
   Lipidmizellen und/oder
   Lipoproteinmizellen und/oder
   Lipid-stabilisierte Emulsionen und/oder
   Cyclodextrine und/oder
   Blockcopolymermizellen und/oder
   Polymermikropartikel und/oder
   Polymernanopartikel und/oder
   Polymerlipidhybridsysteme und/oder
   derivatisierte Einzelkettenpolymere.

7. Zusammensetzung nach einem der Ansprüche 1 bis 6, wobei das erste und das zweite Mittel co-verkapselt sind.

8. Zusammensetzung nach einem der Ansprüche 1 bis 7, wobei das Molverhältnis des ersten Mittels zu dem zweiten Mittel eine nicht-antagonistische, cytotoxische oder cytostatische Wirkung für relevante Zellen in Kultur über wenigstens 5% des Konzentrationsbereichs aufweist, bei dem >1% der Zellen in einem *in vitro*-Assay auf die cytotoxische oder cytostatische Wirkung affiziert werden.

9. Zusammensetzung nach Anspruch 8, wobei die nicht-antagonistische Wirkung über wenigstens 5% des Konzentrationsbereichs gezeigt wird, bei dem 10-90% der Zellen in dem in *vitro*-Assay affiziert werden.

10. Zusammensetzung nach Anspruch 9, wobei die nicht-antagonistische Wirkung über wenigstens 5% des Konzentrationsbereichs gezeigt wird, bei dem 20-80% der Zellen in dem *in vitro*-Assay affiziert werden.

11. Zusammensetzung nach Anspruch 10, wobei die nicht-antagonistische Wirkung über wenigstens 20% des Konzentrationsbereichs gezeigt wird, bei dem 20-80% der Zellen in dem *in vitro*-Assay affiziert werden.

12. Zusammensetzung nach einem der Ansprüche 1 bis 11, die, wenn sie einem Subjekt verabreicht wird, eine therapeutische Aktivität bereitstellt, die größer ist als die, die erreicht wird, wenn die Mittel im selben Verhältnis, aber nicht assoziiert mit Abgabevehikeln, verabreicht werden.